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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/698,323	10/27/2000	Jeffrey M. Isner	47624DIV(71417)	6299

21874 7590 11/12/2009

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EXAMINER	
KAUFMAN, CLAIRE M	
ART UNIT	PAPER NUMBER
1646	

MAIL DATE	DELIVERY MODE
11/12/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/698,323	ISNER ET AL.	
	Examiner	Art Unit	
	CLAIRE KAUFMAN	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 June 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *50,52,55-63,65-68,70,72-78 and 84* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *0,52,55-63,65-68,70,72-78 and 84* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 June 2009* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments

The provisional rejection of claims under the judicially created doctrine of obviousness-type double patenting over claims of copending Application No. 10/714,574 is withdrawn because the claims of the copending application require administration of a nucleic acid.

The rejection of claims 52 and 84 under 35 USC 112, second paragraph, for the indefiniteness of the term "increasing frequency" is withdrawn in view of Applicants' arguments. Specifically, the citation in the specification from page 6, lines 12-15, describing the phrase as "EPC enrichment".

The rejection of claims 52 and 84 under 35 USC 112, second paragraph, for being incomplete is withdrawn in view of the amendment to the claims.

The rejection of claim 68 under 35 USC 112, second paragraph, is withdrawn in view of the amendment to the claim.

Specification

It is maintained for reasons of record that the title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested:

Method for inducing new blood vessels with VEGF and GM-CSF.

Applicants argue that a plain reading of 37 CFR 1.72(a) does not require the title to specify the claimed invention. The argument has been fully considered, but is not persuasive. While the regulation itself is silent with respect to having the title reflect the invention claimed, the MPEP in interpreting the rule provides direct instructions for the examiner. In MPEP § 606.01 [R-2] it is stated, "Where the title is not descriptive of the invention claimed, the examiner should require the substitution of a new title that is clearly indicative of the invention to which the claims are directed."

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 50, 55-63, 65-67 and 84 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3-4 and 11 of U.S. Patent No. 5,980,887 for the reasons set forth in the previous Office Action.

Claims 50, 55-63, 65-67 and 84 remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 49-52, 54-59, 62-65 and 68-69 of the copending Application No. 10/696,391 for the reasons set forth in the previous Office Action.

Claims 50, 52, 55-63, 65-68, 70, 72-78 and 84 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 5,980,887 in view of Boussilino (Path. Res. Pract. 190:834-839, 1994) and Asahara et al. (Science 275:964-967, Feb 1997, cited on the IDS filed 1/18/02) for the reasons set forth in the previous Office Action.

Applicants' intention of addressing the double patenting rejections upon indication of otherwise allowable subject matter is acknowledged.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 50, 53, 55-63, 65-68, 70, 72-78 and 84 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reasons set forth in the previous Office action.

Applicants argue (2nd and 3rd full paragraphs of p. 11 of response) the term "GM-CSF" as used in the specification requires substantial identity to the sequence of human GM-CSF as disclosed, *e.g.,* in WO 86/00639 ('639) or the native sequence or single amino acid substituted (at Leu-23) form disclosed in US 5,229,496 ('496). Additionally '639 and '496 teach a variety of assays for evaluating functionality of any GM-CSF analog. The instant specification also teaches how to make GM-CSF analogs with substantial identity to human GM-CSF and how to identify functional analogs and Exhibits A and B show that altering amino acid sequences of GM-CSF and identifying functional analogs, was well known in the art at the time the application was filed. The argument has been fully considered, but is not persuasive. Unfortunately, no Exhibits A and B accompanied Applicants' reply nor was an Information Disclosure Statement submitted with art to support Applicants' statements. The specification does not have a limiting definition of "GM-CSF", but as stated in the previous Office action includes "proteins having substantial sequence identity to a published human GM-CSF". 'Make and test' is not the standard for the written description requirement, so that the presence of assays in the specification or prior art to allow identification of other "GM-CSF" proteins does not satisfy the requirements. Further, Von Feldt et al. (Immunol. Res. 13(2-3):96-109, 1994) discuss

the complex structure of GM-CSF, which is characterized as having a four-helix bundle core structure, as well as discussing the three synthetic peptides analogs of GM-CSF prepared which all turned out to have antagonist activity. However, the "GM-CSF" of the instant invention must have agonist activity. This further supports the difficulty in being able to readily envision GM-CSF molecules of the invention other than known GM-SCF proteins and GM-CSF proteins which differ from the wildtype with from 1-5 amino acids changes and which remain a full functional equivalent of the wildtype protein as set forth in the original rejection.

Applicants argue (paragraph bridging pages 11-12) that experimentation to alter the amino acid sequence of GM-CSF and identify functional analogs was common and would have been considered routine and not undue (*In re Wands,* 8 USPQ2d 1406) and considered enabled. The argument has been fully considered, but is not persuasive. This argument is moot since there is currently no enablement rejection over the claimed invention. Applicant is reminded that *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111 (Fed. Cir. 1991) at 1115, makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision.

Applicants argue (1st full paragraph of p. 12 of response) "that the specification that any GM-CSF having substantial identity would be expected to work in the methods of the invention." One skilled in the art would have appreciated that Applicants were in possession of methods of inducing neovascularization by administering GM-CSF. Based on the specification and general knowledge available, the skilled artisan would have been able to make and use the invention across the entire scope of the claims without undue burden or experimentation." The argument has been fully considered, but is not persuasive. While the skilled artisan would have recognized that Applicants were in possession of the claimed method using GM-CSF molecules known at the time, including those differing by 1-5 amino acids from wildtype GM-CSF, it is maintained that the inventors were not in possession of the claimed method that relied upon GM-CSF analogs not disclosed in the specification or prior art and the skilled artisan would not have been able to envision those other analogs.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 50, 52, 55-63, 65-68, 70, 72-78 and 84 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ferrara et al. (US 5,332,671, PTO-892 mailed 1/23/08) in view of Bussolino et al. (Path. Res. Pract. 190:834-839, 1994) and Orazi et al. (Blood, 79(10):2610-2619, 1992) for the reasons set forth in the previous Office action.

Applicants argue (middle of p. 13) that Ferrara et al. fails to teach or suggest the use of VEGF in treating chronic or acute ischemia and does not "describe the use of VEGF to **induce blood vessel growth** in any mammalian system." (emphasis added by Applicants) Ferrara et al. only show proliferation of bovine endothelial cells in culture (Example 3, col. 27, lines 12-20). Ferrara merely speculates that "VEGF **may potentially** play a role as a soluble mediator of endothelial cell growth and angiogenesis." (emphasis added by Applicants, col. 30, lines 25-27). Ferrara et al. do not provide motivation for treatment as claimed in the instant invention. The argument has been fully considered, but is not persuasive. Ferrara et al. shows that VEGF induces blood vessel growth in at least two ways. The bovine cells used *in vitro* were capillary cells, and the conclusion of the experimental results was that, "This demonstrates that the growth factor is not just an endothelial cell mitogen, but is actually able to trigger the entire chain of events leading to new blood vessel formation...." (Example V, col. 28, line 68 through col. 29, line 5). Also, in the chick chorioallantoic *in vivo* system, VEGF produced, "A marked angiogenic response with radial growth of blood vessels toward the Sephadex beads" in 85% of the VEGF compared to 10% of control eggs (Example III, col. 27, lines 37-42). While not explicitly stated, the implication of the disclosed therapeutic uses (col. 6, lines 1-12, and col. 14, lines 20-31), such as for wounds and diabetic ulcers, appears to be for induction of blood vessel

growth at the site of trauma. While Ferrara et al. is silent with respect to treating ischemia, it was well known at the time that diabetic ulcers, for example, are in general ischemic (*e.g.*, Grunfeld, Adv. Intern. Med. 37:103, 1992, abstract). It is maintained that Ferrara et al. teaches VEGF for induction of blood vessel growth and provides a suggestion and motivation for its use in the treatment of conditions caused by ischemia.

Applicants argue that Bussolino does not describe methods for inducing new blood vessel growth or reducing or preventing the severity of blood vessel damage using VEGF and GM-CSF and, therefore, does not remedy the deficiencies of Ferrara. Bussolino fails to teach or suggest administering VEGF or GM-CSF for induction of new blood vessel growth for treatment of ischemia or to treat or prevent blood vessel damage related to ischemia. Nor does Bussolino teach or suggest administering VEGF or GM-CSF in combination. The argument has been fully considered, but is not persuasive. Bussolino teaches (p. 835, end of col. 1) that *in vitro* it has been shown that GM-CSF "induce[s] endothelial cells functions related to angiogenesis. It includes the stimulation of proliferation…" And as quoted in the previous Office actoin (sentence bridging pages 9-10), "They also state (p. 835, col. 2, first full paragraph), "The primary effect of GM-CSF and G-CSF on vasculature *in vivo* is the stimulation of the angiogenesis process…."" Bussolino et al. is relied upon for the teaching of the action of GM-CSF on angiogenesis, *i.e.*, the formation and differentiation of blood vessels, not directly for the treatment of ischemic conditions. Also, this is not an anticipatory reference, but relied upon in combination with other references for suggesting administration of both VEGF and GM-CSF. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicants argue Orazi also fails to teach or suggest the combination of VEGF and GM-CSF. Nor is there a teaching or suggestion of administration to treat or prevent an ischemic condition. The argument has been fully considered, but is not persuasive. Orazi is relied upon for the teaching of administration of GM-CSF and the finding that in response to GM-CSF bone marrow vascular network increased in branching, tortuosity and dilation, supporting the effects of GM-CSF on increased blood vessel growth. As with the other two references, Orazi is not relied upon alone, but in combination with the other references to show obviousness. Because

both VEGF and GM-CSF were shown to induce blood vessel growth and ischemic conditions were known in which an increase in blood vessel growth would be advantageous (*e.g.,* see Ferarra), it would have been obvious to use VEGF and GM-CSF for their known and expected properties to induce blood vessel growth in situations in which that would be therapeutically beneficial with a reasonable expectation of success.

Prior Art

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Banai et al. (Circulation, 89:2183-2189m 1994) showed that when VEGF was administered to dogs with gradual occlusion of the left circumflex coronary artery over a 28-day treatment period, there was a 40% increase in collateral blood flow and an 89% increase in the density of intramyocardial distribution vessels (p. 2187, col. 2, end of first paragraph). It was concluded that the effect of VEGF was either from radial growth of preexisting arterioles and/or vascular sprouting (p. 2188, beginning of col. 2). Despite differences between dogs and humans, the authors conclude, "Nonetheless, these results suggest a novel and potentially important therapeutic approach to patients with ischemic heart disease…."

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire Kaufman, whose telephone number is (571) 272-0873. Dr. Kaufman can generally be reached Monday, Tuesday, Thursday and Friday from 9:30AM to 2:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached at (571) 272-0835.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Official papers filed by fax should be directed to (571) 273-8300. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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November 6, 2009

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